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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,430	12/10/2001	Mark J. Graham	RTS-0341	2753

7590 10/03/2002

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	6

DATE MAILED: 10/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/006,430	Applicant(s) GRAHAM ET AL.	
	Examiner Mary Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-15 and 21-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 12-15* is/are rejected.

7)☒ Claim(s) *3 and 21-32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1, 2, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by N_Genseq database AAX37224 (July 07, 1999).

Claims 1, 2, 12 and 14 are drawn to compositions comprising 16 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

N_Genseq database AAX37224 teaches a sequence of 38 bases which has bases 13-38 complementary to base 820-845 of instant SEQ ID NO: 3. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 26 base contiguous homology with instant SEQ ID NO:3.. Note also MPEP 2112.01

which states that "if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." N_Genseq database AAX37224 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

3. Claims 1, 2, 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by GenEmbl database AX004400 (August 24, 2000).

Claims 1, 2, 12 and 14 are drawn to compositions comprising 16 to 50 nucleobases targeted to CD81 including antisense compositions. Claims 12 and 14 are included in the instant art rejection since the limitation therein "pharmaceutically acceptable carrier or diluent" is not considered to breath new life and meaning into what appears to be a claim to an otherwise known prior art nucleic acid, absent evidence to the contrary.

GenEmbl database AX004400 teaches a sequence of 26 bases which has bases 820-845 of instant SEQ ID NO: 3. Absent evidence to the contrary, the sequence disclosed in the prior art would have an expectation to function as an antisense to CD81 due to the 26 base contiguous homology with instant SEQ ID NO:3. Note also MPEP 2112.01 which states that "if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." GenEmbl database AX004400 teaches an oligonucleotide having the claimed structure, and thus reads on the instant invention as claimed.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-10 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oren et al (IDS Reference AH) and Tsitsikov et al. (PNAS Vol. 94, pp. 10844-10849, 9/1997), in view of the collection of Agrawal et al. (Molecular Medicine Today, Vol. 6, 2/00, pages 72-81), Bennett et al. (Chapter 2, pages 13-46, from Methods in Molecular Medicine: Antisense Therapeutics, 1996), Baracchini et al. (U.S. Patent 5,801,154) and Cowsert (U.S. Patent 5,951,455).

Claim 1 is drawn to a compound 16 to 50 nucleobases in length targeted to a 3'-untranslated region, a coding region, a stop codon region, or a 5'-untranslated region of a nucleic

acid molecule encoding CD81 of SEQ ID NO:3, an intron 1 region, an intron 2 region, an intron 3 region, and intron:exon junction region, an exon 1 region, or an exon 8 region of a nucleic acid molecule encoding human CD81 of SEQ ID NO:11, or a 3'-untranslated region of a nucleic acid molecule encoding human CD81 of SEQ ID NO:10, wherein said compound specifically hybridizes with one of said regions of said nucleic acid molecule encoding CD81 and inhibits the expression of CD81. Claim 2 is drawn to the compound of claim 1 which is an antisense oligonucleotide. Claim 4 is drawn to the compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified internucleoside linkage. Claim 5 is drawn to the compound of claim 4 wherein the modified internucleoside linkage is a phosphorothioate linkage. Claim 6 is drawn to the the compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified sugar moiety. Claim 7 is drawn to the compound of claim 6 wherein the modified sugar moiety is a 2'-O-methoxyethyl sugar moiety. Claim 8 is drawn to the compound of claim 2 wherein the antisense oligonucleotide comprises at least one modified nucleobase. Claim 9 is drawn to the compound of claim 8 wherein the modified nucleobase is a 5-methylcytosine. Claim 10 is drawn to the compound of claim 2 wherein the antisense oligonucleotide is a chimeric oligonucleotide. Claim 12 is drawn to a composition comprising th3e compound of claim 1 and a pharmaceutically acceptable carrier or diluent. Claim 13 is drawn to the composition of claim 12 further comprising a colloidal dispersion system. Claim 14 is drawn to the composition of claim 12 wherein the compound is an antisense oligonucleotide.

Claim 15 is drawn to a method of inhibiting the expression of CD81 in cells or tissues *in vitro* with the compound of claim 1 so that expression of CD81 is inhibited.

Oren et al. are relied upon to teach the nucleotide sequence of CD81, also known as tapa-1 (see page 4011). They do not specifically teach design or use of antisense oligonucleotides for the further characterization of CD81.

Tsitsikov et al. is relied upon to teach CD81-deficient mice and the motivation to inhibit CD81 expression as a tool in discovering what physiological effects are observed upon inhibition of the CD81 gene. They do not specifically teach antisense as the tool for inhibiting CD81 expression.

Agrawal et al. are relied upon to teach generically the design of antisense to any known target gene. Specifically they teach "antisense oligonucleotides have also become efficient molecular biological tools to investigate the function of any protein in the cell." (Abstract) They also teach mechanisms for antisense to design to any target (see Figure 3 on page 76 for instance), including modifications to antisense for optimal performance (see pages 77-79). They do not specifically teach antisense to CD81.

Bennett et al. are relied upon to teach that "the antisense paradigm offers the opportunity to identify rapidly lead compounds based on knowledge of the biology of a disease process, and a relevant target gene sequence. With this information, the practitioner of antisense drug discovery can rapidly design, synthesize, and test a series of compounds in cell culture and determine if the

target gene is specifically inhibited." (Page 13) They provide the overall process for design and use of antisense oligonucleotides based on the knowledge of a target gene sequence and administration of the designed antisense compounds to cells in culture, but do not provide specific motivation for design of antisense to CD81.

Baracchini et al. and Cowsert et al. are both relied upon to teach design of antisense oligonucleotides to a known gene target and modifications of said antisense for improved function *in vitro*. Specifically, Baracchini et al. teach in cols. 4-10 the motivation to design antisense to a known gene target and methods for modifying said antisense for increased expression. Cowsert et al. teach in cols. 3-12 and 25-32 teach the motivation to design antisense to a known gene target and methods for modifying said antisense for increased expression. Cowsert specifically teaches design of an antisense having 8 to 30 bases (see claim 1). Cowsert taught in columns 3-4, targeting specifically the following claimed regions: 3'-untranslated region, coding region, stop codon region, 5'-untranslated region, intron regions, exon regions, and intron:exon junctions. They further teach methods of using said antisense in cells in cell culture (Cowsert col. 35). They teach the claimed modifications of antisense as follows: modified internucleoside linkage; phosphorothioate linkage; at least one modified sugar moiety; a 2'-O-methoxyethyl sugar moiety; at least one modified nucleobase; a 5-methylcytosine base (Cowsert col. 25-col. 34). They also teach a chimeric oligonucleotide (Cowsert col. 33) and pharmaceutical compositions of the claimed compounds including use of colloidal dispersion

systems such as liposomes (Baracchini et al. Col. 4, lines 23-64). They do not specifically teach design of antisense to CD81 genes as instantly claimed.

It would have been *prima facie* obvious to one of ordinary skill in the art to design an antisense to the CD81 gene (Oren et al.) having as a tool for the investigation of the expressed protein function (Agrawal et al.), or for the identification of drug candidates (Bennett et al.). Bennett et al. taught design of antisense to any known gene target and testing said antisense in cells in culture. One of ordinary skill in the art would have been motivated to inhibit the CD81 gene since Tsitsikov et al. taught inhibition of this gene to study the physiological effects. Since Agrawal, Bennett et al., Cowsert and Baracchini et al. all taught the benefits for use of antisense to inhibit a gene for study of gene function in cells in cell culture, one of ordinary skill in the art would have been motivated to design antisense to the CD81 gene as taught by Oren et al. for instance, for the further study of CD81. One of ordinary skill in the art would have been further motivated to design the optimal size and known chemical modifications of antisense routinely used in the art taught by Agrawal et al., Cowsert and Baracchini et al. such as modified internucleoside linkage; phosphorothioate linkage; at least one modified sugar moiety; a 2'-O-methoxyethyl sugar moiety; at least one modified nucleobase; a 5-methylcytosine base (Cowsert col. 25-col. 34), a chimeric oligonucleotide (Cowsert col. 33) and pharmaceutical compositions of the claimed compounds including use of colloidal dispersion systems such as liposomes for improved antisense stability inside the cell.

One of ordinary skill in the art would have also had an expectation of success to design such antisense sequences to CD81 sequences since Bennett et al., Agrawal et al., Cowsert and Baracchini et al. all taught that the design of an antisense requires the target gene sequence optionally complexed with modifications thereof for improved inhibition of the target gene in cells in culture.

5. Claims 3 and 21-32 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The art does not teach nor fairly suggest nucleic acid compositions comprising the claimed SEQ ID NOS. in claim 3 nor the dependent claims 21-32.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
October 1, 2002